REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-93 were presented for examination. Claims 1-40, 47-49, 52-65, and 74-77 were previously cancelled. Claim 45 is cancelled in this Amendment.

Claims 86-89 have been withdrawn from consideration. Applicant requests that these method claims be rejoined after a product claim from which they depend has been allowed.

Thus, claims 41-44, 46, 50-51, 66-73, 78-85, and 90-93 are presented for reconsideration.

Claim 93 has been amended by changing the type font for "Gag, Pol, and Env" so that it is consistent with the remaining claims. *See, e.g.*, claim 90.

Claim Objections

Claims 43 and 45 were objected to under 37 CFR § 1.75(c), as being in improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that the recitation of a polynucleotide comprising the cPPT and CTS regions derived from an HIV-type retrovirus in claim 43 and the recitation of a cis-acting central initiation region (cPPT) and the termination region (CTS) of an HIV-1 retroviral genome in claim 45 do not further limit the phrase "wherein the cPPT and CTS are derived from a retrotransposon" in base claim 41. While Applicant courteously disagrees with the rejection, claim 45 has been cancelled. Thus, the objections may be withdrawn.

Double Patenting

The provisional nonstatutory double patenting rejection of 41-45, 51, 66-70, 73, 78-85, and 90-93 as being unpatentable over claims 36, 39, 41, 43-45, 52, and 69-73 of copending Application No. 10/313,038 was maintained. Office Action at 3. Applicant respectfully requests that this provisional ground of rejection be held in abeyance pending an indication of allowable claims in one of these applications. See MPEP § 1504.06.

Claim Rejections - 35 USC § 103

The Examiner rejected claims 41-46, 50, 51, 66-73, 78-85, and 90-93 under 35 U.S.C. § 103(a) as being unpatentable over Verma *et al.* (WO 97/12622, hereinafter "Verma") in view of Charneau *et al.* (1994, hereinafter "Charneau '94"), and Charneau *et al.* (1992, hereinafter "Charneau '92"), as evidenced by Giovannangeli *et al.* (1997, hereinafter "Giovannangeli"). Office Action at 3. This ground for rejection is respectfully traversed.

The prior art does not disclose all of the elements of Applicant's claims

Applicant's claims are directed to a recombinant, non-replicative, non-infectious, lentiviral transfer vector containing the nucleotides that form the central triplex DNA. The claims require cPPT and CTS sequences that are out of the natural context in the lentiviral genome because "the vector is deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins." (Specification at p. 2, ll. 6-8, and p. 8., ll. 1-4.)

It should be apparent from Applicant's claims that Applicant's vector, and the other embodiments of the invention incorporating the vector, contain, among other things, three distinct elements:

(1) a lentiviral vector containing functional cPPT and CTS sequences,

(2) a lentiviral vector that is deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins, and

(3) a defined nucleotide sequence, e.g., a transgene or sequence of interest, for transfer into the nucleus of a cell.

According to the Examiner, all the claimed elements were known in the prior art, as taught by Verma, Charneau '92, and Charneau '94. Office Action at 9. Applicant courteously disagrees. All of the claim elements are not shown in the cited prior art.

None of the cited references describes a lentiviral vector containing functional cPPT and CTS sequences without functional genes encoding lentiviral Gag, Pol, and Env proteins. Indeed, none of the cited references discloses anything other than the cPPT and CTS sequences in their native environment of a complete retroviral genome.

Specifically, Verma describes a "Packaging Construct" in Fig. 1 containing a *pol* gene. In this context, it is important to understand that the cPPT and CTS sequences are part of the *pol* gene. See Applicant's response filed March 9, 2007, at page 34. This Packaging Construct does not contain functional cPPT and CTS sequences in a "vector . . . deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins" as recited in Applicant's claims. Instead, Verma's vector contains cPPT and CTS sequences *and* a functional *pol* gene.

Charneau '92 and Charneau '94 describe functional cPPT and CTS sequences, but only in the context of the complete lentiviral genomes. These references do not describe cPPT and CTS sequences "deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins" as recited in Applicant's claims.

And finally, there is no teaching or suggestion in the Giovannangeli reference of functional cPPT and CTS sequences in a vector "deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins."

The Examiner placed great emphasis on the *structure* of the vector as claimed, Office Action at 7, but the Examiner has not addressed these structural limitations in the claims. If the Examiner adheres to the rejection, she is requested to provide evidence showing that functional cPPT and CTS sequences, out of their context in the retroviral genome, were known in the art prior to Applicant's invention.[1]

Meanwhile, Applicant submits that a *prima facie* case of obviousness has not been established because the cited art does not describe or support all of the elements of Applicant's claims. The rejection should be withdrawn for this reason alone.

There would have been no reason to modify Verma's vectors to include two CPPT-CTS sequences

The Examiner further contends that it would have been obvious to modify the Verma retroviral transfer vector by inserting the cPPT and CTS sequences of Charneau '92 and Charneau '94 into Verma's vector to improve transfer, integration, and sustained long-term expression of the transgene inside a cell. Office Action at 5-6. Applicant respectfully disagrees.

[1] The Examiner has not established the scope and content of the prior art in this regard. Applicant submits that, prior to its invention, cPPT and CTS sequences were employed in a full viral context, not in a context where the sequences were deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins. *See* Fuentes *et al.*, "Strand Displacement Synthesis in the Central Polypurine Tract Region of HIV-1 Promotes DNA to DNA Strand Transfer recombination," Biol. Chem. 47:29605-29611 (1996); *Kupiec, et al.*, "reverse transcriptase jumps and gaps," J. Gen. Virol., 77:1987-1991 (1996); and *Lavigne, et al.*, "DNA Curvature Controls Termination of Plus Strand DNA Synthesis at the Centre of HIV-1 Genome," J. Mol. Biol., 266:507-524 (1997).

Importantly, there are no findings of fact that cPPT and CTS sequences were known to improve "transfer, integration and sustained long-term expression of a transgene inside a cell" as alleged by the Examiner.

Nonetheless, the Examiner's transgene expression system would have *two cPPT-CTS sequences* as is apparent from the Verma reference. The Verma reference contains the following relevant teachings:

> The method of the invention includes the combination of a minimum of three vectors in order to produce a recombinant virion or recombinant retrovirus. A first vector provides a nucleic acid encoding a viral gag and a viral pol. . . . Most preferably, the viral gag and pol are derived from a lentivirus, and most preferably from HIV.
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> * * *
>
> A second vector provides a nucleic acid encoding a viral envelope (env). The env gene can be derived from any virus, including retroviruses.
>
> * * *
>
> A third vector provides the cis-acting viral sequences necessary for the viral life cycle. Such sequences include the Ψ packaging sequence, reverse transcription signals, integration signals, viral promoter, enhancer, and polyadenylation sequences. The third vector also contains a cloning site for a heterologous nucleic acid sequence to be transferred to a non-dividing cell.

Verma at 5- 6.

A schematic illustration of Verma's vectors for expression of the transgene is shown in Fig. 1, which appears as follows:

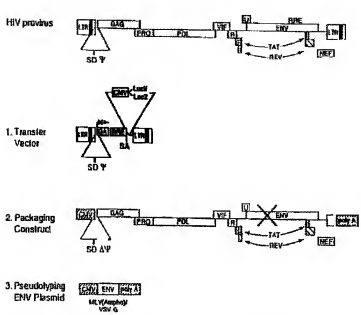

Figure 1

The vector identified as "2. Packaging Construct" in Fig. 1 contains the *pol* gene and thus contains the cPPT and CTS sequences, because the cPPT and CTS sequences are part of the *pol* gene.

The Examiner alleges that a person of ordinary skill in the art would have added Charneau's cPPT and CTS sequences to the vector that Verma identifies as the "1. Transfer Vector" in Fig. 1. This would have resulted in *two cPPT-CTS sequences* in Verma's vectors for expression of the transgene.

Applicant submits that there would have been no reason why a person skilled in the art would have modified Verma's vector to contain *two cPPT-CTS sequences*. If the Examiner adheres to the rejection, she is requested to provide findings of fact and a reasonable basis for making such a modification.

The result of adding two, CPPT-CTS sequences to Verma's vectors would have been unpredictable

Meanwhile, the Examiner alleges that adding cPPT-CTS sequences to Verma's vector would "yield predictable results," Office Action at 12, as evidenced by improved transfer of the vector to the cell; in other words, a second cPPT-CTS sequence in the vectors is better than one. Such is not the case.

Rijck et al. reported that introduction of a second cPPT-CTS sequence into a lentiviral vector resulted in the presence of two triplex sequences ("DNA flaps"), but no higher transduction efficiency. *See* Rijck et al., "The central DNA flap of the human immunodeficiency virus type 1 is important for viral replication," Biochem. and Biophys., Res. Comm., 349:1100-1110 (2006). The authors concluded that "the presence of one DNA flap is sufficient and that its role is not cumulative." *Id.* at 1108.

The only conclusion is that it would not have been obvious to introduce a second cPPT-CTS sequence into Verma's vectors with the expectation of obtaining a predictable result. There is no evidence of record to support any other conclusion.

As Judge Rich, writing for a majority of the court *In re Papesch* said:

> If that which appears at first blush to be obvious though new is shown by evidence not to be obvious then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall.

In re Papesch, 137 U.S.P.Q. at 43, 48 (C.C.P.A. 1963). Here, the evidence in the Rijck reference prevails over the surmise that providing two cPPT and CTS sequences would have yielded predictable results. The rejection based on obviousness must fail for this additional reason.

In view of the foregoing remarks, Applicant submits that the claimed invention is neither anticipated nor rendered obvious by the cited references. Applicant therefore

requests the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Finally, Applicant submits that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Please grant any additional extensions of time required to enter the attached reply and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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